Remarks / Arguments

Claim Objections 35 USC 112

Claims 52 and 53 were rejected under 35 USC 112 as being indefinite.

Claims 52 and 53 have been amended so as to replace "the target" by "the target area" as suggested by the Examiner.

Claim Rejections 35 USC 103

Claims 1 to 18, 20 to 28, 36, 38 and 49 to 53 were rejected under 35 USC 103 (a) as being unpatentable over *Coffee et al* (WO 98/03267) in view of *Shastri et al* (WO 97/16545).

Claim 1

Claim 1 as amended is directed to a method of enabling growth of mammalian cells, which method comprises: supplying liquid comprising biologically compatible polymer to a liquid outlet in the vicinity of a surface and subjecting liquid issuing from the outlet to an electric field to cause the liquid to form polymer fibre which is attracted to and deposits onto the surface to form a polymer fibre scaffold comprising a three-dimensional continuous network of intercommunicating fibre portions having a given fibre diameter with gaps between adjacent fibre portions; and applying mammalian cells to the fibre scaffold, the method further comprising selecting a size of the gaps between the fibre portions and a size of the fibre diameter relative to a diameter of the mammalian cells so as to facilitate at least one cell process selected from the group consisting of growth preferentially along the fibre portions, attachment to the fibre portions, elongation preferentially along the fibre portions, and differentiation.

Coffee et al is not concerned with enabling growth of mammalian cells. Rather, *Coffee et al* is primarily concerned with formation of wound dressings to protect a wound while allowing air to pass through the dressing and pus or other detritus to pass from the wound while preventing ingress of bacterial or matter into the wound (see the paragraph

bridging pages 17 and 18). There is no disclosure in *Coffee et al* that the gaps between the fibres portions and the fibre diameter should have a size relative to diameter of mammalian cells so as to facilitate at least one cell process as set out in claim 1. Rather, *Coffee et al* discusses many different fibre diameters and gives very large ranges for the possible fibre diameter, for example from a few nanometres to over 100 micrometres (see page 17 of *Coffee et al*). *Coffee et al* thus would clearly teach to the person skilled in the art that the specific fibre diameter is of no importance. There is even less teaching in *Coffee et al* regarding any gap between the fibres. Indeed, *Coffee et al* is completely silent as to the sizes of the gaps between the fibre portions.

To summarize:

1. *Coffee et al* is not concerned with enabling growth of mammalian cells;

2. Coffee et al, by discussing many different fibre diameters and wide ranges of fibre diameters, clearly teaches to the skilled person that the actual fibre diameter is not important;

3. *Coffee et al* gives no fibre gap data;

4. *Coffee et al* teaches nothing whatsoever about the relationship between fibre diameter and fibre gap;

5. *Coffee et al* does not teach selecting a size of the gaps between the fibre portions and a size of the fibre diameter relative to a diameter of the mammalian cells so as to facilitate at least one cell process.

Thus, nothing whatsoever in *Coffee et al* teaches the subject matter of amended claim 1. Certainly there is no disclosure or suggestion in *Coffee et al* of selecting a size of the gaps between fibre portions and the size of the fibre diameter relative to a diameter of mammalian cells so as to facilitate at least one cell process selected from the group consisting of growth preferentially along the fibre portions, attachment to the fibre portions, elongation preferentially along the fibre portions, and differentiation.

As regards *Shastri et al* (WO 97/16545), this document is concerned solely with the use of electrically conductive biocompatible polymers to achieve electrical stimulation of nerve cells. *Shastri et al* describes numerous methods for synthesising the polymer but does not even hint at the use of an electric field to cause liquid to form a polymer fibre which is attracted to and deposits onto a surface to form a polymer fibre scaffold comprising a three-dimensional continuous network of intercommunicating fibre portions having a given fibre diameter with gaps between adjacent fire portions. Rather, in *Shastri et al* the electrically conducting polymer may be a coating on or can be blended with polymers forming culture flasks, wells, beads, or other culture containers (see for example page 16 lines 7 to 10).

To summarize:

1. *Shastri et al* requires that the polymer be electrically conducting;

2. *Shastri et al* teaches that the nature of the substrate is not important, it does not even have to be porous let alone fibrous;

3. *Shastri et al* nowhere hints at the use of an electric field to produce fibre from a liquid;

4. *Shastri et al* teaches nothing whatsoever about the relationship between fibre diameter and fibre gap;

5. *Shastri et al* does not teach selecting a size of the gaps between the fibre portions and a size of the fibre diameter relative to a diameter of the mammalian cells so as to facilitate at least one cell process.

Absent the hindsight available to the Examiner from having read the application as filed, a person skilled in the art would not even consider trying to combine the disclosures of *Shastri et al* and *Coffee et al* because they are concerned with very different issues, that is *Coffee et al* is concerned with production of wound dressings whereas *Shastri et al* is concerned with the use of electrically conductive polymers to enable electrical stimulation of nervous cells. Moreover, neither *Coffee et al* nor *Shastri et al* teaches or

even hints that the physical properties of a substrate may be important to enable growth of mammalian cells. *Coffee et al* is silent on this point whilst *Shastri et al points* in a completely different direction, namely to the use of electrically conductive polymer substrates that may be non-porous.

Even if the person skilled in the art were specifically directed to try and combine the disclosures of *Coffee et al* and *Shastri et al* with full knowledge of the claimed invention, he would not be able to arrive at the claimed invention because claimed features absent from *Coffee et al* are not present in *Shastri et al* and vice versa. Thus, to take examples, neither *Coffee et al* nor *Shastri et al* teaches anything about the relationship between fibre diameter and fibre gap or even hints at selecting a size of the gaps between the fibre portions and a size of the fibre diameter relative to a diameter of the mammalian cells so as to facilitate at least one cell process, as required by claim 1. Rather *Coffee et al* discusses a large range of fibre diameters and is silent about the fibre gap size while Shastri teaches that what is crucial is that the polymer is electrically conducting and that the physical nature of the substrate is not important, rather it could even be non-porous.

Neither *Coffee et al* nor *Shastri et al* in any way teaches that the physical properties of polymer fibre may facilitate at least one cell process. Coffee is silent on this point. Moreover, *Coffee et al* attaches no importance to the particular fibre diameter, is completely silent about fibre gap size and certainly does not in anyway suggest an importance to the relationship between fibre diameter and fibre gap size. As regards *Shastri et al*, the teaching of this reference is that the substrate must formed of an electrically conductive polymer (that is it is the electrical properties of the substrate that are important), and that the physical nature of the substrate is not important, it may even be non-porous (that is there is no fibre) *Shastri et al* thus teaches in a very different direction to the claimed invention.

The inventive contribution made by the inventors of the present application and claimed in claim 1 is simply not taught or even hinted at by *Coffee et al* and *Shastri et al*.

The subject matter of claim 1 is thus patentable over the cited documents.

Claims 2 to 13

These claims are dependent on claim 1 and should be allowable for the same reasons as claim 1.

Claim 14

Claim 14 is directed to a method of facilitating at least one cell process of human fibroblast cells, which method comprises: supplying liquid comprising a biologically compatible polymer to a liquid outlet in the vicinity of a surface and subjecting liquid issuing from the outlet to an electric field to cause the liquid to form polymer fibre which is attracted to and deposits onto the surface to form a polymer fibre scaffold comprising a three-dimensional continuous network of intercommunicating fibre portions having a fibre diameter with gaps between adjacent fibre portions; and applying the human fibroblast cells to the fibre scaffold, the method further comprising selecting the fibre diameter to be in a range of 1 to 2 microns and selecting a size of the gaps between the fibre portions such that the human fibroblast cells grow or elongate preferentially along the fibre of the fibre scaffold, wherein the biologically compatible polymer is selected from the group consisting of: a composition comprising ethyl acetate, isopropyl alcohol, amyl acetate, isobutyl alcohol, denatured alcohol, camphor and nitrocellulose, and polylactide.

For the reasons set out above in relation to claim 1, nothing in *Coffee et al* or *Shastri et al* would lead a person skilled in the art to this subject matter claimed in claim 14. For example, neither *Coffee et al* nor *Shastri et al* teaches anything about the relationship between fibre diameter and fibre gap let alone even hints at selecting a fibre diameter to be in a range of 1 to 2 microns and selecting a size of gaps between fibre portions such that human fibroblast cells grow or elongate preferentially along the fibre of the fibre scaffold. *Coffee et al* is not concerned with cell processes let alone with facilitating at least one cell process of human fibroblast cells, is silent about the fibre gap size, and discusses a large range of fibre diameters indicating clearly that fibre diameter is not important while *Shastri et al* teaches that what is crucial is that the polymer substrate is electrically conducting and that the physical nature of the substrate is not important, it may even be non-porous, that is there is no fibre.

Neither *Coffee et al* nor *Shastri et al* in any way teaches that the physical properties of polymer fibre may facilitate at least one cell process. Coffee is silent on this point, attaches no importance to the particular fibre diameter, is completely silent about fibre gap size and certainly does not in anyway suggest an importance to the relationship between fibre diameter and fibre gap size. As regards *Shastri et al*, the teaching of this reference is that the substrate must formed of an electrically conductive polymer (that is it is the electrical properties of the substrate that are important), and that the physical nature of the substrate is not important, it may even be non-porous (that is there is no fibre) Shastri *et al* thus teaches in a very different direction to the claimed invention.

As in the case of claim 1, even if the person skilled in the art was specifically directed to try and combine the disclosures of *Coffee et al* and *Shastri et al* with full knowledge of the claimed invention, he would not be able to arrive at the subject matter of claim 14 because claimed features absent from *Coffee et al* are not present in *Shastri et al* and vice versa.

Claim 16

Claim 16 is directed to a method of providing an environment for facilitating differentiation of stem cells, which method comprises: supplying liquid comprising a biologically compatible polymer to a liquid outlet in the vicinity of a surface; subjecting liquid issuing from the outlet to an electric field to cause the liquid to form polymer fibre which is attracted to and deposits onto the substrate to form a polymer fibre scaffold comprising a three-dimensional continuous network of intercommunicating fibre portions; and selecting a fibre diameter and a gap between fibre portions that, without addition of extrinsic biological factors, facilitate differentiation.

Coffee et al does not teach anything about cell differentiation let alone teach selecting the physical properties of a network of intercommunicating fibre portions to, without addition of extrinsic biological factors, facilitate differentiation. *Shastri et al* teaches nothing about the importance of the physical properties of the substrate but rather is concerned solely with its electrical properties.

For the reasons explained above in relation to claim 1, neither *Coffee et al* nor *Shastri et al* teaches the subject matter of claim 16. Neither *Coffee et al* nor *Shastri et al* in any way teaches that the physical properties of polymer fibre may facilitate cell differentiation. Coffee is silent on this point, attaches no importance to the particular fibre diameter, is completely silent about fibre gap size and certainly does not in anyway suggest an importance to the relationship between fibre diameter and fibre gap size. As regards *Shastri et al*, the teaching of this reference is that the substrate must formed of an electrically conductive polymer (that is it is the electrical properties of the substrate that are important) and that the physical nature of the substrate is not important, it may even be non-porous (that is there is no fibre) Shastri *et al* thus teaches in a very different direction to the claimed invention. Furthermore, neither *Coffee et al* nor *Shastri et al* teaches selecting a fibre diameter and a gap between fibre portions that, without addition of extrinsic biological factors, facilitate differentiation.

As in the case of claim 1, even if the person skilled in the art was specifically directed to try and combine the disclosures of *Coffee et al* and *Shastri et al* with full knowledge of the claimed invention, he would not be able to arrive at the subject matter of claim 16 because claimed features absent from *Coffee et al* are not present in *Shastri et al* and vice versa.

Claim 17

Claim 17 is dependent on claim 16 and should be allowable for the same reasons as claim 16.

Claim 18

Claim 18 is directed to a method of facilitating differentiation of osteogenic stem cells, which method comprises supplying liquid comprising a biologically compatible polymer to a liquid outlet in the vicinity of a surface and subjecting liquid issuing from the outlet to an electric field to cause the liquid to form polymer fibre which is attracted to and deposits onto the substrate to form a polymer fibre scaffold comprising a three-dimensional continuous network of intercommunicating fibre portions, the method further comprising selecting a fibre diameter of about 10 microns and selecting gaps between

adjacent fibre portions of about 16 microns and applying the cells to the fibre scaffold without addition of extrinsic biological factors, the selecting of the fibre diameter and gaps resulting, after a period of time, in the cells having a morphology resembling nerve cells.

For the reasons explained above in relation to claim 1, neither *Coffee et al* nor *Shastri et al* teaches the subject matter of claim 18. Neither *Coffee et al* nor *Shastri et al* in any way teaches that the physical properties of a polymer fibre network may facilitate at least one cell process, let alone that selecting a fibre diameter of about 10 microns and a gap size of about 16 microns may facilitate differentiation of osteogenic stem cells. *Coffee et al* is completely silent on this point. Moreover, *Coffee et al* attaches no importance to the particular fibre diameter, is completely silent about fibre gap size and certainly does not in anyway suggest an importance to the relationship between fibre diameter and fibre gap size. As regards *Shastri et al*, the teaching of this reference is that the substrate must formed of an electrically conductive polymer (that is it is the electrical properties of the substrate that are important), and that the physical nature of the substrate is not important, it may even be non-porous (that is there is no fibre) Shastri *et al* thus teaches in a very different direction to the claimed invention.

Thus, as in the case of claim 1, even if the person skilled in the art was specifically directed to try and combine the disclosures of *Coffee et al* and *Shastri et al* with full knowledge of the claimed invention, he would not be able to arrive at the subject matter of claim 18 because claimed features absent from *Coffee et al* are not present in *Shastri et al* and vice versa.

Claim 19

Claim 19 is dependent on claim 16 and should be allowable for the same reasons as claim 16.

Claim 20

Claim 20 is directed to a method of facilitating at least one cell process of mammalian cells, which method comprises: supplying liquid comprising a solution of a biologically

compatible polymer to a liquid outlet in the vicinity of a surface and subjecting liquid issuing from the outlet to an electric field to cause the liquid to form polymer fibre which is attracted to and deposits onto the substrate to form a polymer fibre scaffold comprising a three-dimensional continuous network of intercommunicating fibre portions, the method further comprising selecting a fibre diameter in the range from 0.2 to 100 microns and a gap size between adjacent fibre portions in the range from about 10 to 500 microns; and applying mammalian cells to the fibre scaffold, the selecting of the fibre diameter and gap size facilitating at least one cell process selected from the group consisting of growth preferentially along the fibre portions, attachment to the fibre portions, elongation preferentially along the fibre portions, and differentiation.

For the reasons explained above, neither *Coffee et al* nor *Shastri et al* teaches the subject matter of claim 20. Neither *Coffee et al* nor *Shastri et al* in any way teaches that the physical properties of a polymer fibre network may facilitate at least one cell process, let alone that selecting a fibre diameter in the range from 0.2 to 100 microns and a gap size between fibre portions to the range from about 10 to 500 microns selecting a fibre diameter of about 10 microns and a gap size of about 16 microns may facilitate at least one cell process of mammalian cells. *Coffee et al* is completely silent on this point. Moreover, *Coffee et al* attaches no importance to the particular fibre diameter, is completely silent about fibre gap size and certainly does not in anyway suggest an importance to the relationship between fibre diameter and fibre gap size. As regards *Shastri et al*, the teaching of this reference is that the substrate must formed of an electrically conductive polymer (that is it is the electrical properties of the substrate that are important) and that the physical nature of the substrate is not important, it may even be non-porous (that is there is no fibre).

Thus, as in the case of claim 1, even if the person skilled in the art was specifically directed to try and combine the disclosures of *Coffee et al* and *Shastri et al* with full knowledge of the claimed invention, he would not be able to arrive at the subject matter of claim 20 because claimed features absent from *Coffee et al* are not present in *Shastri et al* and vice versa.

Claim 21

Claim 21 is directed to method of facilitating at least one cell process of mammalian cells, which method comprises: supplying liquid comprising a biologically compatible polymer melt to a liquid outlet in the vicinity of a surface and subjecting liquid issuing from the outlet to an electric field to cause the liquid to form polymer fibre which is attracted to and deposits onto the substrate to form a polymer fibre scaffold comprising a three-dimensional continuous network of intercommunicating fibre portions, the method further comprising selecting a fibre diameter in the range from 2 to 500 microns and a gap size between adjacent fibre portions in the range from about 25 to 3000 microns and applying mammalian cells to the fibre scaffold, the selecting of the fibre diameter and gap size facilitating at least one cell process selected from the group consisting of growth preferentially along the fibre portions, attachment to the fibre portions, elongation preferentially along the fibre portions, and differentiation.

For the reasons explained above, neither *Coffee et al* nor *Shastri et al* teaches the subject matter of claim 21. Neither *Coffee et al* nor *Shastri et al* in any way teaches that the physical properties of a polymer fibre network may facilitate at least one cell process of mammalian cells, let alone that selecting a fibre diameter in the range from 2 to 500 microns and a gap size between fibre portions in the range from about 25 to 3000 microns may facilitate at least one cell process of mammalian cells at least one cell process selected from the group consisting of growth preferentially along the fibre portions, attachment to the fibre portions, elongation preferentially along the fibre portions, and differentiation. *Coffee et al* is completely silent on this point. Moreover, *Coffee et al* attaches no importance to the particular fibre diameter, is completely silent about fibre gap size and certainly does not in anyway suggest an importance to the relationship between fibre diameter and fibre gap size. As regards *Shastri et al*, the teaching of this reference is that the substrate must formed of an electrically conductive polymer (that is it is the electrical properties of the substrate that are important) and that the physical nature of the substrate is not important, it may even be non-porous (that is there is no fibre).

Thus, as in the case of claim 1, even if the person skilled in the art was specifically directed to try and combine the disclosures of *Coffee et al* and *Shastri et al* with full

knowledge of the claimed invention, he would not be able to arrive at the subject matter of claim 21 because claimed features absent from *Coffee et al* are not present in *Shastri et al* and vice versa.

Claims 15, 22 and 23

Claim 15 is dependent on claim 20 and should be allowable for the same reasons as claim 20 while claims 22 and 23 are dependent on claim1 and should be allowable for the same reasons as claim 1.

Claim 24

Claim 24 is directed to a method of forming a fibre scaffold for facilitating at least one cell process of mammalian cells, which method comprises: supplying comprising biologically compatible molten or liquid polymer to a liquid outlet in the vicinity of a surface and subjecting liquid issuing from the outlet to an electric field to cause the liquid to form polymer fibre which is attracted to and deposits onto the substrate to form a polymer fibre-scaffold comprising a three-dimensional continuous network of intercommunicating fibre portions, the method comprising selecting, so as to facilitate at least one cell process of mammalian cells, a fibre diameter in the range of from 20 to 70 microns and a gap size between adjacent fibre portions in the range of 100 to 500 microns.

For the reasons set out above in relation to the earlier independent claims, neither *Coffee et al* nor *Shastri et al* teaches that the physical properties (fibre diameter and fibre gap size) of a fibre scaffold can facilitate at least one cell process of mammalian cells let alone hints at selecting a fibre diameter in the range from 20 to 70 microns and a gap size between adjacent fibre portions in the range of 100 to 500 microns. *Coffee et al* attaches no importance to the particular fibre diameter, is completely silent about fibre gap size and certainly does not in anyway suggest an importance to the relationship between fibre diameter and fibre gap size. As regards *Shastri et al*, the teaching of this reference is that the substrate must formed of an electrically conductive polymer, that is it is the electrical properties of the substrate that are important and that the substrate may be non-porous, i.e. non-fibrous. *Shastri et al* thus teaches in a very different direction to the claimed invention.

Thus, as in the case of claim 1, even if the person skilled in the art was specifically directed to try and combine the disclosures of *Coffee et al* and *Shastri et al* with full knowledge of the claimed invention, he would not be able to arrive at the subject matter of claim 24 because claimed features absent from *Coffee et al* are not present in *Shastri et al* and vice versa.

Claims 25, 26, 27 to 30, 35 and 36

Claims 25 and 26 are dependent on claim 24 and should be allowable for the same reasons as claim 24 while claims 27 to 30 are dependent on claim 1 and should be allowable for the same reasons as claim 1. Claims 35 and 36 are also dependent on claim 1 and should be allowable for the same reasons as claim 1.

Claims 49 to 53

Claims 49 to 53 are dependent, directly or indirectly, on one of the above mentioned independent claims and should be allowable for the same reasons as the corresponding independent claims.

Claims 1 to 30, 35, 36 and 49 to 53

Claims 1 to 30, 35, 36 and 49 to 53 were rejected under 35 USC 103 (A) as being unpatentable over *Coffee et al* and *Shastri et al* in view of *Smith et al* (WO 01/27365) and *Simpson et al* (WO 02/40242).

Nothing in Smith et al or *Simpson et al* provides the features of the independent claims missing from *Coffee et al* and *Shastri et al*.

Smith et al is concerned with keeping wounds clean and simply teaches that poly (caprolactone) may be used for formation of the wound dressing. *Smith et al* does not provide the features of the independent claims missing from *Coffee et al* and *Shastri et al*. For example, *Smith et al* neither teaches nor hints that the physical properties of a substrate may be important to enable growth of mammalian cells and certainly neither

teaches or hints at selecting fibre diameter and fibre gap size to facilitate at least one cell process.

As regards the very lengthy *Simpson et al,* this reference is concerned specifically with the electro-processing of collagen. *Simpson et al* adds nothing to the teaching of *Coffee et al* and *Shastri et al*. For example, nothing in *Simpson et al* teaches or hints that the physical properties of a substrate may be important to enable growth of mammalian cells and certainly nothing in *Simpson et al* teaches or hints at selecting fibre diameter and fibre gap size of a fibre network or scaffold to facilitate at least one cell process.

Conclusion

Based on the amendments and arguments above, it is respectfully submitted that the Examiner's rejections have been overcome and that this application is now in condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the rejections and to issue a Notice of Allowance.

If there are any questions regarding these amendments and remarks, Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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